DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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CIRCULATORY SYSTEM DEVICES PANEL

OPEN SESSION

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Monday, April 23, 2001

9:00 a.m.

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C O N T E N T S

PROCEEDINGS

Call to Order

DR. TRACY: I would like to call to order this session of the Circulatory Systems Devices Panel. The topic today is discussion of a premarket application for Sulzer IntraTherapeutics IntraCoil Self-Expanding Peripheral Stent, used in the treatment of stenotic or occluded femoral or popliteal arteries.

MS. MOYNAHAN: I would like to read the conflict of interest statement for this morning. The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety.

To determine if any conflict exists, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. The agency has determined that participation of certain members and consultants outweighs the potential for a conflict of

interest of the government. Therefore, waivers have been granted for Dr. Janet Wittes and Anne Roberts for their interest in firms that could potentially be affected by the panel's recommendations. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency also took into consideration other matters regarding Dr. Roberts, Cynthia Tracy, Julie Freischlag, Warren Laskey, Tony Simmons and Kenneth Najarian. These panelists reported interests in firms at issue but in matters that are now concluded, unrelated to today's agenda or limited to an employing institution. The agency has determined, therefore, that they may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons

making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. TRACY: I would like to have the panel members introduce themselves please.

MR. JARVIS: Gary Jarvis, industry rep.

DR. NAJARIAN: Ken Najarian, Associate Professor or Radiology, University of Vermont.

DR. AZIZ: Salim Aziz, University of Colorado, cardiovascular surgeon; associate professor.

DR. WITTES: Janet Wittes, biostatistician, Statistics Collaborative.

DR. SIMMONS: Tony Simmons, Wake Forest University, cardiologist.

DR. LASKEY: Warren Laskey, University of Maryland, interventional cardiologist.

DR. TRACY: Cynthia Tracy, Georgetown University, electrophysiologist.

MS. MOYNAHAN: Megan Moynahan, Executive Secretary of the Circulatory System Devices Panel.

DR. FREISCHLAG: Julie Freischlag, Chief of Vascular Surgery and a vascular surgeon at UCLA.

DR. DEWEESE: Jim DeWeese, University of Rochester, Cardiac and Vascular Surgical Chief.

DR. ROBERTS: Anne Roberts, Professor of Interventional Radiology at University of California, San Diego.

MR. DILLARD: Jim Dillard. I am the Director of the Division of Cardiovascular and Respiratory Devices.

MS. MOYNAHAN: This is the appointment to temporary voting status for today: Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27th, 1990, as amended April 18th, 1999, I appoint the following people as voting members of the Circulatory System Devices Panel for this meeting, on April 23rd, 2001: James DeWeese, Kenneth Najarian, Anne Roberts and Tony Simmons.

For the record, these people are special government employees and are consultants to the panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review, and have reviewed the material to be considered at this meeting. It is signed by David W. Feigal, Director of the Center for Devices and Radiological Health.

DR. TRACY: It is time to move on to the open public hearing. Is there anybody who has

requested to speak this morning? Anybody else who would like to make a statement in the open public hearing at this point?

[No response]

Then, we will close the open public hearing. Since there is nobody who wishes to speak this morning -- I think there are people who are reserving their comments for later, we will move on to the sponsor's presentation at this time.

MS. MOYNAHAN: I would like to remind the sponsor, if they could please introduce each speaker and state whatever conflict of interest they might have, which includes whether the travel was paid for by the company or whether they were an investigator in the study.

Sponsor Presentation

MS. BRITTLE: Good morning. I am Maria Brittle, Regulatory Affairs Manager at Sulzer IntraTherapeutics. On behalf of our company, I would like to thank the panel and FDA for the review of the IntraCoil stent as we pursue a market approval for a femoropopliteal indication.

[Slide]

We have several individuals in attendance to present information and answer questions.

First, from the company we have Randy La Bounty, Director of Clinical Affairs, and Dan Desaulnier, Operations Manager and former Senior R&D engineer for the IntraCoil stent.

Representing CDAC, the Data Management Center at Harvard University, is Dr. Richard Kuntz. Finally, the IntraCoil stent trial will be presented today by Dr. Kenneth Rosenfield and Dr. Gary Ansel. Dr. Rosenfield is Director of Interventional Vascular Suite at St. Elizabeth's Medical Center and Assistant Professor of Medicine at the Tufts University School of Medicine. He was principal investigator for the IntraCoil stent trial.

Dr. Gary Ansel is Director of Peripheral Vascular Intervention at Grant/Riverside Methodist Hospitals, Assistant Clinical Professor of Medicine at Medical College of Ohio. Grant/Riverside was one of our higher enrolling centers.

[Slide]

Dr. Rosenfield will cover background on femoropopliteal disease, device description and the trial summary. Dr. Ansel will cover clinical scenarios and observations.

Now I am pleased to turn the podium over

to Dr. Rosenfield.

DR. ROSENFIELD: Thank you, Maria. Thank you, the panel, for giving me the opportunity to speak this morning on behalf of the IntraCoil.

[Slide]

First I would like to make the disclosure that during the conduct of this trial I was compensated as a member of the sponsor's medical advisory board though I had no connection with or influence over outcomes or data management, and currently there are no existing conflicts, financial or otherwise. For this panel meeting, I am being compensated for my travel expenses, hotel and time away from my clinical practice.

[Slide]

We are going to start with reviewing a little bit of the background of femoropopliteal disease.

[Slide]

As many of you who are clinicians on the panel acknowledge, the superficial femoral and popliteal arteries, which we will consider really as one for the purposes of this parenteral, and often the clinical scenarios are also considered as a single entity, is really the Achilles heel of the

vascular specialist. It is probably the most likely peripheral vessel in the body to contain disease. There is often a very high plaque burden. Diffuse involvement of the vessel is commonplace. There is a high prevalence of primary occlusion, and it is one of the most difficult vessels in the body to treat effectively, in terms of maintaining long-term patency, both percutaneously and surgically.

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From the standpoint of the surgeon, surgical treatment is effective but is often associated with significant morbidity and mortality. The use of a venous conduit in a patient population who has significant coronary-artery disease in whom you may wish to preserve that conduit for coronary bypass grafting, and the durability is certainly suboptimal. Compared to other locations, for example aortal bifemoral bypass, femoropopliteal bypass is not nearly as durable. When a graft fails in the femoropopliteal position, it can often be associated with significant risk to the limb.

[Slide]

On the other hand, endovascular treatment

also is plagued with high restenosis rates. This is data from the TASC document which is a meta-analysis combining several trials. In the yellow, you can see that comparing the patency, in the upper two boxes, of the iliac lesion revascularization using percutaneous or endovascular techniques is much superior to that in the femoral artery.

[Slide]

Now, there are currently two stents that have been approved by the FDA for use in vascular applications. Those include the Palmaz stent, which is a balloon expandable stent, and the self-expanding WallStent. These are approved for suboptimal result after balloon angioplasty in the iliac arteries.

[Slide]

There have been attempts made by various investigators to use these approved devices for vascular applications in the femoropopliteal access to see if we can improve upon those suboptimal results after balloon angioplasty. The first trial I will describe is the femoral artery stent trial which used the balloon expandable Palmaz stent in the femoropopliteal artery, directly comparing it,

in a randomized fashion, to balloon angioplasty alone. This trial was discontinued very shortly into its course after the finding of restenosis due to stent compression in the femoral artery, primarily in the adductor canal in the lower portion of the thigh.

[Slide]

Likewise, there have been attempts to use the self-expanding WallStent to try to confer a better patency on the results of endovascular therapy, and these two trials summarize the representative results of many trials which document that there is, in Conroy's study, about 47 percent primary patency, meaning without any further intervention at one year there was 47 percent patency. With additional intervention you could improve that and additional invasive procedure, bringing it up to 79 percent.

The same is true in Martin's study using WallStents. This was a multicenter trial, with 61 percent primary patency; 84 percent secondary patency, with a fairly high complication rate of about 17 percent.

[Slide]

Using the current device that is before

the FDA panel, this is the first trial that suggested that this particular device may be able to confer a better long-term patency, a better result using this stent over balloon angioplasty alone. This trial was performed my Michelle Henry, in Europe. It was a single-center study, involving 73 patients, using the self-expanding IntraCoil stent and showing a one-year patency of 85 percent; secondary patency of 88 percent.

[Slide]

So, let's just describe the device here.

[Slide]

This is a stent that was designed for application in tortuous vessels subject to external compression, inflection or elongation. It is a coil-shaped stent that is self-expanding, made of nitinol, as opposed to stainless steel which is the case with the WallStent. It is a single wire construction with round tips at the ends to prevent any sharp edges, and it is highly flexible, very deliverable. It bends and rotates in concert with the vessel.

[Slide]

It is delivered on an over-the-wire delivery system. It is constrained. The stent is

wound tightly to the delivery system, here on the right. It is wound tightly on the delivery system. It is constrained at the two edges and, in order to deliver the stent, one pulls these two handles in sequence to release the two ends of the stent.

These are the sizes that were available in the trial, between 4 mm and 8 mm, all 40 mm in length. When there was a lesion that was longer than 40 mm it required overlapping on tandem stents.

[Slide]

These are the sizes that were available for the early portion of the trial. There was only a 63 cm length catheter available. That required an antegrade puncture on the same side as the actual lesion. In the latter portion of the trial we had available a longer catheter for contralateral delivery.

[Slide]

So, let's get into the results of the trial.

[Slide]

The objective of the trial was to compare the safety and efficacy of the IntraCoil stent versus balloon angioplasty alone for

femoropopliteal arteries. The primary endpoints were to identify angiographic restenosis, greater than 50 percent narrowing at 9 months and MACE or major adverse clinical events at 9 months, including death, peri-operative Q wave MI and clinically driven target lesion revascularization.

[Slide]

In addition, we identified several major secondary endpoints that we thought were of importance. The first and probably the most important is could we get patients through the procedure successfully and safely. So, the major complication rate at 30 days we felt was an important endpoint to look at. Then, was there any hemodynamic benefit that would be conferred on patients who received the stent as opposed to balloon angioplasty. For that, we elected to look at the change in ABI from baseline to the 9-month endpoint in both groups.

[Slide]

Assumptions that were made for this trial included the fact that restenosis for PTA alone would be about 50 percent; that restenosis for stenting would be about 37 percent, and we thought we would accrue a 25 percent benefit over stenting.

And, the third assumption was that this would be powered to 80 percent.

The study design that came out was a randomized, multi-center trial with 480 patients. It was calculated to require 480 patients to get to that power and show a statistically significant difference. There was stratification at the point of randomization for diabetics versus non-diabetics.

[Slide]

These are the major inclusion criteria. I won't go through each one individually but they basically are the typical patients that we see that undergo endovascular and, to some degree, surgical repair for femoropopliteal disease -- symptomatic patients with leg ischemia.

[Slide]

These were the major exclusion criteria. We excluded patients with terrible inflow or outflow and very small vessels.

[Slide]

This is the way the procedure went if you were an investigator. This is how you enrolled patients. You obtained the informed consent. You obtained an angiogram to confirm eligibility. They

you crossed the lesion with a guide wire. After you did that you would randomize the patient to getting a conventional PTA, in which case you dilate the vessel to the diameter of the reference vessel. You would take another angiogram. You would try to optimize the results of the angioplasty using the standard methods such as multiple dilatations, increasing pressure or time, or a larger balloon size if you had an unacceptable result. So, you pushed the case until you got a reasonable result and you took a final angiogram.

If you were randomized to stent, then you dilated the patient's vessel to the diameter of the reference vessel. You would then deploy a stent; post-dilate and get a final angiogram.

[Slide]

Now, crossover, importantly, was limited in this trial for PTA patients crossing over to stent. It was limited to patients who developed a limb-threatening situation despite repeated balloon inflations or who had abrupt closure or impending closure of the vessel.

In order to cross over from stent to the balloon group you had to have either thrombus after pre-dilatation that would not resolve or inability,

of course, to properly deploy the stent.

[Slide]

The trial was initiated in March of 1997. The study enrollment was terminated in December of 199 due to slow enrollment. This trial suffered from the same problem that many coronary stent trials have suffered from and now iliac stent trials are suffering from, which is that there is a great reluctance on the part of investigators to enroll patients in a trial that is randomized between balloon angioplasty and stent deployment, especially for the longer and more difficult lesions. I think investigators realized early on that as the off-label stents became available it became more and more difficult ethically to randomize patients when they felt that they were getting more optimal results with stenting. So, as a result of that, the trial was terminated.

[Slide]

There were 266 patients that were enrolled in the randomized phase of this trial from a total of 20 centers.

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These are the patient characteristics. It is important to note that they make up the typical

cohort of peripheral vascular patients which many of us all see, which tend to be a very sick cohort. Specifically, for example, there was about 38 percent diabetics, which is about 2.5 times what you see in a typical coronary stent trial. Likewise, more than three-quarters were smokers, again a very high number.

On the right are the baseline lesion characteristics. Again, you can note that the vast majority of lesions were in the relatively short focal range of less than 3 cm. We believe that also reflected an increasing reluctance on the part of investigators to enroll patients with the more diffuse and difficult lesions to manage with balloon angioplasty alone.

[Slide]

This data shows the procedural results based on quantitative analysis. It shows that there is no statistically significant difference between the acute results from balloon angioplasty versus stent deployment. Notably, the device success was very high. There was only 1.7 percent device failure in terms of being able to deploy the stent. So, this stent is very deliverable, very reliable.

There was, importantly, a large discrepancy between the two crossovers. There was only one patient that crossed over from stent to balloon angioplasty, whereas in the PTA group there were 10 patients or 8 percent of patients who crossed over from balloon angioplasty to stent deployment on the basis of a threatened closure situation.

[Slide]

On the right you see the 9-month restenosis results. Now, the rates are high, and the rates are high because there is basically a relatively low follow-up rate. This is not unexpected. In fact, based on ascertainment bias, we know that the smaller number of patients that get followed up is basically the patients that come back with restenosis that get their angiogram. In fact, based on the FDA's own recommendations, anything less than 88 percent follow-up is subject to this problematic ascertainment bias. The data were derived from only 52 percent of the evaluated lesions so we have a problem in that these patients didn't follow-up if they were asymptomatic.

[Slide]

So, we are not sure how valid that data

is, but one thing we do have very valid data with is the clinical follow-up. We have follow-up based on over 85 percent of patients, and what you can see from this is that the results are excellent in the stent group. While they are not statistically different from the PTA group in terms of freedom from clinically driven TLR, there is a slight tendency towards an improvement in the stent group.

I think the most important thing to note, and really it is the essence of this trial, is on the right slide. There are a couple of things to mention. First of all, the results in the PTA group are not really reflective of what you would see for PTA alone. They are reflective of what you see for PTA with the availability of a bail-out strategy. So, these good results were accomplished at the expense of 10 patients having crossed over to the stent arm, and those patients are included in the PTA group because this was an intention-to-treat analysis.

[Slide]

More importantly, on the right, you can see that the good results in the balloon angioplasty group were accomplished at the expense of a major complication rate that was statistically

significantly greater than those in the stent group. So, the bottom line is that the stent result was an outstanding result and it was accomplished with a relatively low major complication rate out to 30 days. That, as a clinician, kind of make sense.

You know, just to back up for a second and say as a clinician we know that if you are going to try and make an optimal balloon angioplasty result, an acceptable balloon angioplasty result, that often takes multiple repeated inflations, repeat dilatations, higher pressure, giving more contrast in between checking the results. It is much easier, and we know this based on millions of stents deployed, to do a balloon angioplasty, place a stent, get a good result and you can leave it at that. You don't have to really push your luck with the patient and with the vessel to try to make an ideal result, an acceptable result.

Let me just add that I think this data, in a sense, confirmed the validity of the reluctance of the investigators to randomize after a certain point because I think there is a difference in safety using a stent, using this stent as opposed to balloon angioplasty alone, and I think the

investigators, as time went on, realized that. So, in a sense, it kind of confirmed what we already believed to be the case.

We also showed that the ABI had a significant improvement in the stent group compared to the balloon group, suggesting that there is an improved hemodynamic outcome if you place a stent as opposed to the balloon angioplasty group alone, at 9 months.

[Slide]

In summary, from the standpoint of acute safety, we believe this trial showed that there is a lower 30-day major complication rate in the stent group compared to balloon angioplasty. That is 1.5 or 8.4 percent. It is safer to place stents than it is to do balloon angioplasty alone.

The IntraCoil stent was necessary to salvage PTA failures and avoid emergency surgery in about 10 patients, 8 percent of patients.

[Slide]

From the standpoint of effectiveness and durability, we showed that the stent group had a high freedom from clinically-driven TLR, 85 percent at 9 months, and there was improvement in the ABI for the IntraCoil stent that was superior to that

of balloon angioplasty, statistically significant again, and this suggests that there were improved flow characteristics for stented lesions versus balloon angioplasty lesions.

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In conclusion, this study result demonstrates that femoropopliteal stenting with the IntraCoil stent is effective in preventing clinical restenosis and preserving distal leg blood flow. The data also show that the IntraCoil stent is safer than PTA for prevention of acute complications.

Thank you very much. I am now going to turn the podium over to my colleague Gary Ansel.

Clinical Scenarios and Observations

DR. ANSEL: Good morning. Thank you for allowing me to participate.

[Slide]

I am Gary Ansel. I am one of the high enrollers in this protocol, and I am also at a very large community hospital. My goal today is to put into perspective whether this device should be utilized at all or whether we should be doing this procedure at all.

[Slide]

My disclosures are very similar to Dr. Rosenfield's. I was compensated as a member of the advisory board during the trial but I had no connection or influence on the outcomes of data management. Currently I have no conflicts whatsoever, and I have no existing financial interest. My expenses and my time away from my current practice will be reimbursed.

[Slide]

When talking about femoral artery stenting, up till now you kind of get a little impression that a femoral is a femoral is a femoral, but the patients aren't the same. You have patients who have claudication versus patients who have limb-threatening ischemia, ulcers, gangrene that, without a doubt, need to have some type of treatment.

[Slide]

From a cardiovascular standpoint, we as healthcare workers have ignored this population and have not been educated as to the need to treat this population. Without a doubt, for patients that have heart disease we recognize the need for risk factor modification. We recognize the needs of this patient population. However, if a patient

went to their primary care physician and said, "you know, doc, I can't walk across the room," or "I can't walk to the mailbox," traditionally the response has been, "I'm sorry to hear about that. How's your eating habits today?" We have totally ignored that.

[Slide]

But if you look at the quality of life survey data that is out there, claudication is not a minor symptom. These patients often are homebound and their activities are very severely limited. If you look at where the average well adult or the average adult falls in this quality of life diagram and then look at where intermittent claudication falls, it is between chronic lung disease and congestive heart failure. So, this is a very real, significant disease pattern for these patients.

[Slide]

We already have a precedent for treating this type of population. We already do total hip and knee replacements for patients who have problems with ambulation, and we don't question that at all.

[Slide]

The surgical procedures for vascular patients with claudication have been limited. Even though they are very effective and the techniques are time tested, the problem is these patients oftentimes have co-morbidities, such as the coronary disease diabetes, which makes their morbidity and mortality significant for the surgical procedure. Thus, surgery is usually limited to limb-threatening ischemia or patients who have occupation only limiting claudication.

[Slide]

Oftentimes you will hear the primary care physicians also state, well, we can just use medicine or conservative therapy, and we are bombarded every day with ads now for these medications in our medical journals but here is the reality. If you do a somewhat fair comparison between placebo, pentoxifylline or Trental, as it is known, cilostazol or Pletal you see that Pletal or cilostazol has been a huge boon. Almost half the patients can have some improvement at 9 months. But if you look at the result in the IntraCoil trial at patients who have clinical efficacy, it is over 85 percent. This is a significant boon to this patient population.

The other problem with medications these days is that even though the ads will tout the ability of the medication to work, the side effects are not rare. This approved drug has almost 30 percent incidence of severe headaches.

[Slide]

Again, these patients aren't just your simple 40- or 50-year old patient who come into the office and often times just say, "doc, I can't walk." That is not who we are talking about.

[Slide]

Especially for stenting, we are talking about patients who have at an advanced age, coexistent coronary disease, diabetes of renal insufficiency and I think these are areas that stenting certainly allows us to offer these patients an effective and safe procedure.

[Slide]

If we want to reduce complications, this is almost a universal rule -- the shorter the procedure time, the better the end result, the better the procedure. With stenting we can get the shortest procedure time because we don't have to work for an optimal result with a balloon and prolonged inflations and multiple dye injections.

It is a very reliable, stable result -- laminar flow; the vessel opens to its fullest extent. It certainly has the least limitation to flow. Dissections are non-existent or should be non-existent; the least amount of contrast agent without a doubt. You do your pre-study. You do your balloon. You place your stent and you do your post-study. This is now an outpatient procedure. Uniformly, at our institution 87 percent of the patients, even with limb-threatening ischemia, who undergo this type of procedure can be treated as outpatients.

[Slide]

How about lesion specific for stenting? Certainly, long occlusions have been shown traditionally in the task force not to respond to stand-alone balloon angioplasty. Flow-limiting dissection and the other options you have, surgery -- suboptimal result. Or, if there is a significant pressure gradient or an unpristine result can be treated with stenting.

[Slide]

Just to show you some video type of examples, this is a very tortuous popliteal artery with bending inflection of the knee. You can see a

tight stenosis at this tortuous segment.

[Slide]

You can see that the IntraCoil easily conforms to this tortuosity, allowing multi-dimensional flection, better than any other stent that is out there can offer.

[Slide]

Just to give you a couple of quick cases, this is a 64-year white male, a diabetic with a history of smoking. Moderate claudication with an ankle-brachial index of 0.78. As you can see, an 85 percent stenosis of the right superficial femoral artery with kind of diffuse segment disease of about 5 cm.

[Slide]

He initially underwent angioplasty with a 6x4 balloon, and although this is very difficult to tell on a still picture, when you run this there is dissection all the way from here all the way to there, and here to here. This lucency area is continued stenosis at that site. By QA it only shows a 25 percent residual stenosis but there is a grade C section that you can't see.

[Slide]

Two IntraCoils were placed. As you can

see, residual stenosis is minimal. The patient was discharged the same day with an asymptomatic, normalized ankle-brachial index of 1.0. Remember, his pre-procedure was 0.78.

[Slide]

As we talked about, these patients oftentimes have coexistent coronary disease, and this patient just happened to come back in with unstable angina after a plaque rupture. As is my habit, I usually like to see what my results are on my study patients. So, we took an angiogram of his leg at that time and you can still see a very pristine effect, almost better looking than after the initial result. This was at two months.

The interesting thing is that during this study, even though we were dealing with a high risk group of patients, nobody had a myocardial infarction and, certainly, this offers a very safe alternative for these patients.

[Slide]

When you see this patient come back at 9 months, even though a QA calculates a 31 percent stenosis at this point, which is a limitation to QA, you can see this really doesn't look much different to the eye than his 2-month angiogram or

his immediate post-procedure angiogram, which goes along with this hemodynamic result of a still normalized ankle-brachial index.

[Slide]

Another case scenario, a 63-year old gentleman with diabetes and current smoker who had a previous myocardial infarction, severe claudication with multi-level vascular disease and occlusion of the right superficial femoral artery as well as, which you don't see, femoropopliteal disease and total occlusion of almost 8 cm.

[Slide]

He underwent a balloon angioplasty with a long balloon and, as you can see, there is still significant residual stenosis. If you would look at the flow through here, it would be suboptimal.

[Slide]

What do you do at this point in time clinically? Well, the trial either randomized to angioplasty or stent placement and currently, without an approved stent, what you do is sit there and say is, well, should I use a larger balloon? Do I do a long balloon inflation? Do I use higher pressure? Do I accept a suboptimal result? Do I use a bunch of more dye to try to get an optimal

result, or do I refer this patient for urgent surgery because it is going to close?

Now, if I have a stent available, like in the trial, you stent and you go home. The patient goes home too, as an outpatient usually. This is, again, a boon to this patient population.

[Slide]

Four IntraCoil stents were placed in an interlocking fashion. You can see the type of residual that you have, very open, wide vessel as you would expect from a stent, with a residual stenosis by QA of 10 percent. Again, the patient was discharged very shortly thereafter with an asymptomatic ankle-brachial index of 0.76 which is reflective of his popliteal disease.

[Slide]

At his 9-month angiogram you can see that he continues to have this pristine result. He awaits approval of the IntraCoil stent to have his other femoral artery treated, again, with an ankle-brachial index that is unchanged at 9 months.

[Slide]

The question is can you do this for suboptimal angioplasty? And, we did look at both the roll-ins and the randomized IntraCoil patients

that had suboptimal results after the initial dilation, which was about 70 patients. The bottom line is that the overall results, as you would expect, are similar to the main analysis.

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In summary, this stent does a lot of things for the clinician. It is flexible. It is durable and it resists compression. It is easily deliverable. As was noted by Dr. Rosenfield, you can put the stent in. It has very low device failure rate. It is a very easy stent to get there now, especially with the longer lengths so you can go around the horn.

The complication rate is hard for you, sitting there as a panel, to appreciate but for the very first part of the study these patients were all getting antegrade sticks which, at least in our institution, always carries a much higher risk of groin complications. In spite of that, we had lower complications versus balloon angioplasty which was done in a contralateral fashion.

I think these characteristics make the IntraCoil stent suitable for use in the femoropopliteal arteries, and I think for patient care and for medical care this should be approved.

Thank you very much.

I am going to now turn it back over to the company who will talk about regulatory matters. Thank you.

Concluding Comments

[Slide]

MS. BRITTLE: As you know from our panel package and the draft labeling, we submitted this PMA with a suboptimal indication. That was based primarily on finding equal performance for the stent and PTA group on both primary endpoints, the MACE and the angiographic restenosis. The study also did show that the conventional PTA can be a good option. If the results are optimal a low rate of target lesion revascularization can be expected.

When the initial PTA result is suboptimal, continued attempts to optimize the result increases the patient's likelihood of complications, increasing that acute complication rate. Treatment of a suboptimal PTA with IntraCoil stent, like the main overall study, resulted in fewer complications while providing a low rate of target lesion revascularization, similar to the PTA control group.

[Slide]

However, because of the acute difference in the safety data at 30 days, we also invite consideration of the primary stent indication. There is a significant improvement in acute safety, and there were no differences in safety and effectiveness at 9 months.

Also, the device has some unique advantages in its flexibility, durability and resistance to compression that make it especially suitable for use in the femoropopliteal artery. Thank you.

DR. TRACY: Does that conclude the sponsor's presentation?

MS. BRITTLE: Yes, it does.

DR. TRACY: Thank you. Then, at this point we will move on to the FDA presentation.

FDA Presentation

MS. DANIELSON: Good morning.

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I am Judy Danielson. I am a reviewer in the Peripheral Vascular Devices Branch of the Office of Device Evaluation, and the lead reviewer for the IntraCoil Self-Expanding Peripheral Stent PMA application. Dr. Paul Chandeysson, the lead medical officer, and I will present the FDA summary

of this application. A discussion of the clinical study results and labeling recommendations will be taken into consideration by FDA in our evaluation of this application.

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This presentation will provide a summary of a non-clinical tests conducted on the IntraCoil stent, provide a summary of the clinical investigation and identify the FDA questions for the panel.

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Before the clinical trial began the IntraCoil stent system was tested in the lab to determine its material biocompatibility; on the bench to determine the mechanical integrity of its design; and in the animal to assess the in vivo performance of the stent.

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Biocompatibility testing performed on the IntraCoil stent and delivery catheter followed the ISO standard 10993-1. This testing evaluated the material for cytotoxicity, sensitization, irritation, implantation, hemolysis, mutagenicity and systemic toxicity. The results demonstrated that both the stent and catheter are biocompatible.

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Bench testing of the IntraCoil stent system followed FDA's guidance document, entitled Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices. The sponsor also conducted additional tests relevant to the specific design of the system.

Bench testing involved the stent alone, the delivery catheter and the combined stent-catheter system. Testing of the stent fell into two categories, material specification and integrity. Material specification testing consists of an analysis of the material and mechanical properties and corrosion resistance of the stent. Integrity testing included uniformity of the deployed stent, radial strength and kink potential. Delivery catheter testing evaluated bond strength and the force required to insert and withdraw the catheter. With the combined stent-catheter system bench testing evaluated the crossing profile, stent retention and the stent release mechanism. All of the test results on the stent, the delivery catheter and the combined stent-catheter system were within an acceptable range.

[Slide]

The IntraCoil stent system was tested in an animal study using the porcine model. Seventeen stents were implanted in 7 animals. Due to sizing issues, the majority of stents were placed in the iliac artery. Three stents were placed in the femoral artery and one stent was placed in the aorta.

Histologic evaluations performed at 1, 3 and 6 months showed patent stents. At 6 months, the average percent occlusion of 11 stents implanted in 4 animals ranged from 9-32 percent. The results of the bench biocompatability and animal testing demonstrated the integrity of the device for its intended use.

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Dr. Chandeysson will now provide an overview of the randomized study, the results and the subgroup analysis.

Overview, Results and Subgroup Analysis

DR. CHANDEYSSON: Good morning. My name is Paul Chandeysson. I am a medical officer in the Peripheral Vascular Devices Branch.

[Slide]

The sponsor has provided data from a

prospective, multi-center, randomized clinical trial of the IntraCoil stent versus PTA in patients with occlusive disease of the superficial femoral artery and/or the popliteal artery. The lesions were up to 15 cm in length if they were stenoses and up to 12 cm if they were occlusions.

The study was intended to support an indication for use of primary stenting of the lesions and, therefore, it used a superiority hypothesis. The estimate of the required sample size was calculated based on the assumption of a reduction in the rate of stenosis of 25 percent, from 50 percent to 37 percent at 9 months. The resulting prospective sample size was about 500 patients, 250 in the stent arm and 250 in the PTA arm.

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In addition to the rate of restenosis at 9 months, a composite primary endpoint of major adverse cardiac events was defined consisting of death, peri-procedural Q wave myocardial infarction and clinically-drive revascularization of the target lesion at 9 months.

[Slide]

Enrollment of patients into the study was

slower than expected, and the study was stopped with only 135 patients randomized to the stent arm and 131 patients randomized to the PTA arm. A total of 266 randomized patients is approximately half of the 500 patients who were to have been randomized. The lesions treated in the study were shorter than was intended, with about 60 percent being 3 cm or less. Apparently, physicians were reluctant to refer patients with longer lesions into the study because it had become practice to stent most longer lesions, using a different stent off-label. The study did not show a statistically significant improvement in the primary effectiveness endpoint resulting from stenting versus PTA alone. However, there were no significant safety concerns.

[Slide]

The sponsor has submitted an application for premarket approval with the indications for use changed to the treatment of abrupt closure or suboptimal PTA. These patients would otherwise undergo an additional procedure such as stenting or surgery. A subgroup of 70 stented patients with 89 lesions was selected based on the presence of a residual stenosis after PTA of at least 50 percent

or dissection of grade C or greater.

[Slide]

The dilatations used in treating the lesions in the subgroup of patients was not the same as that used in treating the patients with PTA alone. The average number of dilatations was 1.8 in the subgroup versus 2.7 in the control group. The average duration of dilatation was 75 seconds in the subgroup compared to 305 seconds in the control group. The average maximum dilatation pressure was 7.9 atmospheres in the subgroup versus 9.4 atmospheres in the control group.

[Slide]

The retrospective analysis of this subgroup of patients showed no significant difference in the rate of adverse events or the primary effectiveness endpoint when compared to the group of patients treated with PTA alone.

[Slide]

The sponsor has submitted an application for premarket approval with the indications for use of stenting of patients with a residual stenosis of at least 50 percent or a dissection of grade C or greater. The subgroup analysis, showing that the safety and effectiveness of the IntraCoil stent in

this group of patients is clinically equivalent to the safety and effectiveness in patients with optimal PTA alone was submitted to support this more limited indication for use.

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The limitations of the subgroup analysis in support of the changed indication for use include the retrospective nature of selecting the subgroup and performing the analysis; the relatively small size of the subgroup; and the difference in the dilatation techniques between the subgroup and the control group.

[Slide]

Ms. Danielson will now pose some questions to the panel.

Questions for the Panel

MS. DANIELSON: The U.S. clinical trial of the IntraCoil stent system was based on primary stenting versus PTA in the clinical treatment of occlusive disease of the superficial femoral and/or popliteal artery.

The sponsor has described why this primary stent study could not be completed. They have also described why they believe a reanalysis of the data supports the use of the IntraCoil stent when the

PTA results are suboptimal. Central to this justification is the suboptimal classification of 70 patients who had a greater than or equal 50 percent stenosis, or a greater than or equal grade C dissection following the pre-dilatation step and prior to placement of the IntraCoil stent.

FDA would like to obtain panel input on the following questions pertaining to the analysis of the clinical data.

[Slide]

Question 1a, please discuss the use of the suboptimal pre-dilatation classification as a surrogate for suboptimal results with PTA.

[Slide]

Question 1b, please discuss any expected differences in terms of clinical outcomes between patients with suboptimal pre-dilatation and patients with suboptimal results from PTA.

[Slide]

Given that the IntraCoil stent data shows improvement in acute safety and no differences in safety and effectiveness at 9 months, please discuss whether there is adequate data for a primary stent indication. If not, what additional information would be necessary to support a primary

stent indication in the femoral and/or popliteal arteries?

[Slide]

The current labeling indicates the use of the IntraCoil stent for the treatment of superficial and or popliteal artery occlusions or stenotic lesions in patients with suboptimal results following PTA. Stents placed in the popliteal artery location are subjected to significant deformations due to flexing of the knee. Bench testing demonstrated adequate kink resistance of the IntraCoil stent. Based on the qualitative analysis of 149 lesions in the randomized study and the 107 lesions in the roll-in patients, IntraCoil stents were placed in 48 popliteal arteries, of which 16 were placed in the suboptimal group.

Question 2 asks the panel to discuss whether the clinical data are adequate to determine the safety and effectiveness of the IntraCoil stent in the popliteal artery.

[Slide]

One aspect of the premarket evaluation of a new product is the review of its labeling. FDA is asking the panel to address the following

questions regarding the product labeling found in section 2 of the panel pack.

Question 3a, please comment on the indications for use section as to whether it identifies the appropriate patient population for treatment with this device.

[Slide]

Question 3b, please comment on the contraindications section as to whether there are conditions under which the device should not be used because the risk clearly outweighs any possible benefit.

[Slide]

Question 3c, please comment on the warnings/precautions section as to whether it identifies all potential hazards regarding the device use.

[Slide]

Question 3d, please comment on the operator's instructions as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Question 3e, do you have any other recommendations regarding the labeling of this device?

[Slide]

The last question, question 4, asks the panel to identify and discuss the items that should be included in a physician's training program for the IntraCoil stent system. Thank you.

DR. TRACY: Thank you. We will move on at this point to the open committee discussion and I will ask Dr. Roberts, who is the lead reviewer, to start us out.

Open Committee Discussion, Recommendations and Voting

DR. ROBERTS: Thank you.

DR. TRACY: I guess the sponsor can come up to that closer table in case we have some direct questions.

DR. ROBERTS: I think that there are obviously a number of questions that this study brings up, and I don't want to take up all of the time because I am sure that other people have questions but perhaps I will just start off with some of the questions that I had with regards to FDA's question number 1.

One of the concerns I have with this, and the first thing I would like to ask is how were these patients who were decided to be put in

suboptimal pre-dilatation classification, how were they chosen?

DR. LABOUNTY: I am Randy Labounty, from Sulzer IntraTherapeutics. They were based upon a conservative type of indication from site-reported data at each investigator site, based upon looking at what the current indications are for iliac stents, which is a 30 percent or greater residual stenosis or flow-limiting dissections or from renal studies which are looking currently at 50 percent or greater residual stenosis.

DR. ROBERTS: So, the investigators at the sites identified patients that they thought would meet these criteria?

DR. LABOUNTY: Not at that time. As Dr. Rosenfield put it in his presentation, the physicians did the initial angioplasty and the results were recorded on the case report form. Then they went ahead and did the stent. We took the data that was originally reported on the case report form and looked at a 50 percent or greater residual stenosis or the dissection that they reported at that time.

DR. ROBERTS: Okay, because first of all, that was quite unclear to me. Also, in looking at

the results, particularly the core lab results, there seems to be a fair number of patients that, for example, were classified by them in the initial data -- I got 21. Granted, there are a lot of numbers in this study but counting it up, I got about 21 type C dissections but only 15 of those were looked at by the core site and they only classified there being 15 in the suboptimal group. I was trying to figure out what happened to the other 6 of those patients. That is why I am a little confused because, certainly, it is one thing to have a nice, clean study when you initially decide how you are going to study these patients, but to go back and sort of start pulling the data out of data that has already been collected -- you know, I think that data then needs to be reviewed very carefully and many of the numbers don't add up, at least when I look at them.

DR. LABOUNTY: I think some of the difference is really in the QA reported versus the site reported data. What is in the patient listings is QA reported data versus what the actual physician thought at the time, which was different compared to what the QA reported. For instance, the site estimated like a final residual stenosis

at the end of the procedure for the stent group as 5 percent versus the QA which had a 25 percent range, and vice versa, for the PTA group the physicians reported a 15 percent residual stenosis at the end of the procedure versus a 25 percent for that.

DR. KUNTZ: My name is Rick Kuntz. I am the Director CDAC that ran this study. I have no conflicts of interest to report, other than I think the travel was paid for me to fly down here.

In this study there was no attempt to identify or prespecify the suboptimal group. The study ended early so there was not sufficient power to show a difference. The reason for the study's termination was, we believe, out of the control of the investigators. Because of increased availability of other stents that are used and the reluctance of people to use balloon angioplasty, the study ground to a halt.

So, the company was faced with using a valid set of about half of the sample size initially envisioned to evaluate, and found that there was no statistical difference between the two groups in the primary endpoint, although a variety of different ways of looking at acute safety

endpoints showed some advantage in some endpoints for stenting and no statistical difference in other safety endpoints.

In an effort to try to understand how this stent could be utilized and be of value to patients, a variety of less than primary stenting indications were sought, one of which would be for use for suboptimal results. The best way to address that was to go back and try to identify a subset of individuals from the retrospective data that the stents could simulate in the stent experience the suboptimal group, and the best way to come up with that was to look at the core laboratory demonstration of dissections during the balloon angioplasty phase of the stent arm, which was a haphazard situation because sometimes the investigators filmed it; sometimes they didn't. The other was to look at the case report form site-reported dissections as the other catchment for that, and using an occlusive set of information which was specified by both the CRS and by the core laboratory we came up with the 70 patients that fit that criteria to represent what we would consider to be a suboptimal result if you were intended to have balloon angioplasty but then got rescued, so-

called, by stenting, all within the stent arm.

So, that was the effort to try to look at the performance of the stent in a group that would be subject to suboptimal results had they been in the PTA arm, and to compare that to the outcomes of the overall study to see if there was any benefit or not. So, it was the best effort to try to take the randomized trials and try to look at the value of the suboptimal results up front by using the intermediate results of balloon angioplasty during the stent procedure.

DR. ROBERTS: But you would agree, I assume, that what you found was not necessarily a real suboptimal result of balloon angioplasty because, presumably, if you looked at the balloon angioplasty results in terms of percent residual stenosis it was only, like, 24 percent residual stenosis in the angioplasty group. But, when you look at this -- I mean, I am assuming since there are only 15 lesions that I could count up that were categorized as type C dissection. That means I am assuming there were 72 other lesions that were ones that were greater than 50 percent stenosis. So, it seems to me, anyway, from looking at this data that the investigators who were doing the angioplasty

really weren't trying to get an optimal angioplasty result. So, to say that this is really a suboptimal angioplasty result is probably not accurate.

DR. KUNTZ: That is absolutely right. What we are left with is that we do know that the balloon angioplasty initial dilatations was equal on both sides. If we look at the characteristics of the balloon selection; if we look at the inflation pressures, the pre-dilatation was equal to that done on balloon angioplasty to begin with. If you then look at the stent use as use for suboptimal result of initial inflation compared to continued balloon angioplasty for the balloon angioplasty arm, you see that the ultimate use of stents was lower in the balloon angioplasty arm. There were 10 patients that ultimately had to have that. But, in order to optimize the balloon angioplasty suboptimal result, one had to use more frequent inflations, more contrast and ultimately ended up with more acute complications.

DR. ROBERTS: I am sorry, everybody keeps referring to more contrast. I didn't actually see where contrast was measured in terms of how much was used.

DR. KUNTZ: Well, we didn't measure contrast specifically. It wasn't prespecified. But the time of inflation was 5 minutes versus 1 minute. The number of inflations was, I think, 4- or 5-fold for balloon angioplasty compared to stenting. It is common to do an angiogram after each inflation. I think there is a pretty solid inference that they received more contrast with the balloon angioplasty for those indications than the stenting arm because of the more frequent inflations, and the probable use of angiograms in between, and the higher incidence of renal failure seen in that arm.

DR. ROBERTS: There was one patient with renal failure in the PTA and zero in the other group. Is that correct or did I miss something.

DR. KUNTZ: Dr. Roberts, you are right with respect to the fact that we looked back at this data and we can't specifically look at that stent arm to determine that that was an intermediary suboptimal group.

But, what we can say is that the natural history of balloon angioplasty which results in good results and suboptimal results in the stent arm was treated more quickly, with fewer

inflations, with less fluoro time and probably less contrast compared to the balloon angioplasty side with more frequent dilatations, and, that that subset, identifying the best we could this initial dissection group with the initial inflation, had similar outcomes overall. So, that is the best analysis we could do retrospective to look at the utility.

DR. ROBERTS: I don't believe -- I may be wrong but I don't believe that I saw time being anywhere in the data in terms of the length of time.

DR. KUNTZ: Sure, that is in there.

DR. ROBERTS: It is? I must say, I didn't see that and, given a fairly high number of patients that had multiple stents placed, and I assume you would do runs in between each stent placing to decide where you were, I suppose that might slow you down a bit as well, plus increase the contrast.

DR. KUNTZ: I think we should put that slide up because I think it will be clearer to you if you see the other parameters that it was likely that more contrast was used. It is a backup slide.

[Slide]

DR. LABOUNTY: And there were 3 renal failures in the PTA group within 30 days and zero in the stent group, and 2 of them did die.

DR. KUNTZ: Let me explain those results. You can see the total time was 1.7 minutes versus 5.1 minutes for PTA, and a higher number of dilatations as well.

DR. ROBERTS: Well, there were 3 renal failures, two of them within 270 days; 1 was within the hospitalization. That was a woman who had a large hematoma and a 4-unit blood loss and, you know, presumably I suppose all of those things might have come into it.

Now, this is the total time of inflation. I meant the total time of the procedure, which I assume is what you were talking about because, obviously, the total time of the inflation is one thing but I had understood that you meant that the time of the procedure was faster so there were less complications because of the time of the procedure being done more quickly. I just didn't see that in the information in here.

DR. ANSEL: I can address that. I am not sure we actually have that information in tabular form, or whatever, but as one of the major

enrollers in this, I think it is pretty common and very forthright that when we were working for an optimal balloon angioplasty result we knew we were going to be in there for a while with these multiple inflations, and it was routine to do an angiogram in between each one of those inflations because the only way you would get the number of inflations is that you were trying to continue to get a better result. If you got a perfect result with one balloon angioplasty you were done. The only reason we would go to an average of 5, and sometimes we did a lot more than 5, is that we were continuing to have suboptimal results.

You know, I think the investigators did a good job in trying really hard, in spite of stents that are available, not to go ahead and use an off-label device and, in fact, in my institution I know of a couple that we left and they closed within 24-48 hours. You know, we were trying to really test this. And, the dye loads always were higher because the routine of doing this procedure with a stent was that you did a balloon inflation to allow one to one optimizing with the blood vessel itself. You then came in with your stent. You post-dilated the stent and took one more angiogram and you were

out of there. So, the dye loads, just by technique, are going to be lower as your time of procedure -- I mean, you can't do 1.8 inflations longer than you can do 5.7. I mean, it just doesn't work out that way.

DR. ROBERTS: When you look at the number of patients who had multiple stents, sometimes up to 6 stents, I am assuming that those patients also took a fair amount of time and a lot of contrast --

DR. ANSEL: I shouldn't have. The routine was that you were stenting based on lesion length. Since you were just pre-dilating, you had initial length of occlusive disease that you knew you were going to treat and you pre-dilated that area and you brought in all your stents.

DR. ROBERTS: I see. So, you didn't even bother to look again --

DR. ANSEL: We didn't bother. No, you did your one angiogram post your pre-dilation but in between each one of those stents there was not a reason to do any other angiograms if there were no problems. So, you know, it was very quick. You just placed your 1 to 4 stents; post-dilated the entire vessel; did your angiogram and you were done.

DR. ROBERTS: I guess I am thinking if there really was a difference in terms of this suboptimal pre-dilatation, presumably with the PTA you should find an increase in the target vessel or target revascularization and, yet, that wasn't found.

DR. ANSEL: I am sorry, I am not sure I know what you are saying.

DR. ROBERTS: Well, since with the PTA alone, you know, with the concept of having a stent in place, that that should give you a better result, then presumably if you were to say that we are really comparing apples and apples here and that the stent really does do something, then I would assume you would expect to see the revascularization decrease in that group and, yet, that was not found.

DR. ANSEL: Well, it depends on how you really look at it because we weren't really comparing stent to only angioplasty. We were comparing stent to angioplasty with stent backup. Ten patients is a lot of patients to cross over to stent in this small subgroup. Without a doubt, that sways these numbers quite a bit. I think it is pretty obvious that if you have somebody who has

a suboptimal result, flow-limiting dissection, you don't have that many options. You either get these stented up or you don't. I think the surrogate of a residual stenosis is still a reasonable one whether you achieve it with one inflation versus five inflations. It is still the same makeup and your end result was the same.

And, I think the reality of it is that even after stenting our results were as good as angioplasty for a very focal lesion. I mean, from a clinician's standpoint, what was in my face and the reason I stopped enrolling is that, you know, I do a ton of these and having a patient every three days have a problem in the angioplasty arm for a very focal stenosis was a problem. I couldn't go to the patient and say I really think you should be in this and I can randomize you to angioplasty when I knew the ones who were getting stents, I almost had no complications with in spite of doing antegrade punctures. Even the techs in my lab were going, you know, pray, pray, pray and they don't ever do that for an antegrade puncture.

So, here we were taking a procedure that should have been a very safe procedure from an angioplasty standpoint and the restenosis rates are

very low, but the safety of the procedure, even though it is lower than what is in the publications, was still a significant difference between what we were getting with the stents. So, just from practicality and patient safety perspective, you couldn't enroll people anymore because you couldn't say, hey, I'm going to give you an 8-fold difference in the complication.

DR. KUNTZ: Let me make one comment. I am not here to advocate the approval of this stent; I want to clarify the issues of the results of the trial. The decision, obviously, is yours about approval. But I think the way that this trial comes out is that it was an underpowered study that stopped early. If you look at the stent results, there was a very good outcome with respect to the acute complications and late-term complications. The PTCA side also had a very good primary endpoint outcome. There is no question about that. And, we can say that this trial showed a benefit and reduction in that. There is no question about that.

The real question about the utility of this is that if there is value in the high rates of freedom from repeat revascularization of 86 percent

at the expense of a low complication rate, which was seen in a variety of different ways of measuring complications, quickness and fewer inflations is of value compared to the PTA arm which also had good results, but possibly more complications on a few dimensions and more time in the lab and potentially more contrast, though not measured. This stent should be valued on those comparative differences. There won't be a difference in the primary endpoint. There is no question about that. And, the attempt to look at suboptimal use was an attempt to understand how we evaluated the PTA arm which actually did have stent backup. That is, if we can show value as a primary indication for elective use, could we say that the PTA arm benefited from having this available as a backup so that aggressive angioplasty could be performed, so that in about 8-10 percent of cases they could be bailed out with the stent as well.

So, there are subtle differences up front to look at the utility of this device, and that is essentially what the data is focusing on, and all the points that you brought up about the major differences are absolutely valid.

DR. ROBERTS: Can I just ask you a

question with regards to these bail-out crossover patients? There seemed to be a moderate discrepancy between what the sites felt was a significant dissection and what you, in the core lab, read as a significant dissection. As a matter of fact, presumably I guess, if you had looked at films when they were coming out you would have said this doesn't need crossover. Can you comment on that? There were nine patients that basically got crossed over to stenting. One went to arterectomy and the other nine went to stenting. Of those, although some of them were read as Ds and Es in terms of dissections, some of those you read as As and Bs, to my recollection.

DR. KUNTZ: Right. There is always a discrepancy between the core lab reads and what the sites say for two reasons. One is that the core lab has a specific way of reading the sections that the sites don't have. The other is that the sites don't film all the worst complications that occur during the case, which is very common. It is not unusual for a dissection to occur and for the investigator not to put it on film when they do their fluoro injection, but they immediately put in a balloon, and we have seen this with coronary

studies and others. So, we really don't know the actual recorded history of all the fluoroscopic angiography that was performed by what is filmed, especially in peripheral studies when you have many times much more complicated events, say, for cineangiography where it is much easier to do those in coronary angiograms. So, we don't know what the actual incidence is.

We do know that the frequency of our complications that we described in the suboptimal was higher than the actual crossovers, suggesting that the threshold that individuals used for crossover did meet the initial prespecified criteria, that is, to use the stent in cases of limb-threatened closures. So, we think that the crossovers, by our review of what is available, actually did meet robust criteria for patients who actually did face limb-threatening ischemia and that the stent was quite valuable in those ten patients up front. So, while it isn't 30 or 40 percent of the cases and represents a small portion, it is still enough, I think, in one way or another to actually improve some of the outcomes of that intention-to-treat PTA arm overall, and when combined with the underpowered aspect of the study,

only reaching half of the sample size, the considerations are that, you know, one should consider whether the stent really did have utility in helping to float that result because of the availability of the stents in both arms.

So, we don't know exactly what the actual dissections were because often they weren't filmed during the case, especially in cases where the site reports that there was a big dissection. They had to put the stent in. They were happy that they opened up the artery and happy that the patient didn't have to go to emergency surgery, and what they filmed was only a class A or class B dissection.

DR. ROSENFIELD: There is one other reason for that discrepancy, a third reason I would say, and that is that a lot of the investigators submitted cut film, the majority actually, and cut film doesn't show dynamic flow and it is conceivable that there might have been a discrepancy between what one could see in the core lab, and the core lab actually measures using quantitative analysis. The automated system measures side to side and doesn't really show anything about the dynamic flow and the

investigator at the site is dependent on seeing that flow and may have established that there was a flow limitation and crossed over on that basis.

DR. ROBERTS: This wasn't brought up by anyone speaking. I don't know whether I am supposed to bring it up or not. We had some data that was submitted to us from a study in the United Kingdom which I didn't hear discussed by anyone. I will look around and see if anybody tells me to be quiet but I guess not.

MS. PETERSON: My name is Amy Peterson. I am Vice President of Regulatory Affairs and an employee of Sulzer IntraTherapeutics. We provided the data to the FDA, as agreed with our contract with the U.K. study center. Under contract, we can't speak about that data here in public. If you would like to go into private session, we would be more than happy to discuss it. They have not published yet and, by contract, it limits our ability to divulge the results of that trial in a public forum.

DR. ROBERTS: Well, I am not going to say that we need to do that now but I think that is going to be important at some point, that the panel have some discussion of what was shown in that.

MS. PETERSON: Do we defer to Megan then?

DR. ROBERTS: Well, let's not interrupt the process now. I think that some of what I would look at in terms of question one, I would sort of want to get a better feeling for what that data might indicate.

Like I said, I don't want to hold this up. I think that in terms of the panel and in terms of question one, I have asked most of the questions that I have. I continue to have a fair concern about whether or not we are sort of going back into data that maybe really doesn't show what we would like to make it show when we are trying to, you know, take that data and put it into something that would support approval of this, and I think there is a problem with that because I am not really sure that it is valid. So, I yield my time for the moment and perhaps we can circle around again and talk about the other questions.

DR. TRACY: Yes, you will have an opportunity again to ask questions. We will move ahead. Dr. DeWeese?

DR. DEWEESE: I have one question. It is my understanding that you selected 69 suboptimal results. Now, these were, by what we received,

based on greater than 50 percent stenosis or dissection. There were only 10 which you had to cross over from the PTA. What I would like to know, if you have the information, is the results of the people that had PTA, how many of them did have, by the same definition, suboptimal results from PTA. We know 10 of them did, but how many more did? I mean, you know, before they left the procedure you do determine --

DR. LABOUNTY: Yes, in the PTA group?

DR. DEWEESE: Yes.

DR. LABOUNTY: You know, again, they were trying to get an optimal result in that group. So, in the majority of the cases, most likely all of them, they did get an optimal result of less than 50 percent residual stenosis but it did occur with higher complication rates and things like that -- you know, additional dilations and things like that.

One thing in the suboptimal angioplasty group that has to be kind of looked at is that there really is no difference in this suboptimal angioplasty group than what has been seen in the WallStent iliac or the Palmaz trial itself. Those suboptimal angioplasty definitions were after a

primary dilation or the initial dilation. So, there really is no difference in this and what is currently going on with the other iliac trials or the renal stent trials right now.

DR. ROBERTS: Can I make one point about that? That is, those are set up prospectively to say that this is a suboptimal result. I mean, you are right. Your criteria were even tighter. They are not going back retrospectively and saying, well, this was a suboptimal result and so now we will count it as a suboptimal result. I mean, that is a prospective suboptimal result and I do think that there is a little bit of a difference there because, like I say, it seems to me that there is an attempt to go back to data. The study wasn't set up this way and to go back to the data and try and pull something out of it in order to make this acceptable -- so, I do think there is a difference there.

DR. DEWEESE: My understanding then is that there were only 10 patients who had a suboptimal result from PTA alone. Is that correct?

DR. ANSEL: Yes, because they should have crossed over to the stent --

DR. DEWEESE: They would have had less

than 50 percent stenosis --

DR. ANSEL: Yes.

DR. DEWEESE: -- and had no dissections.

DR. ANSEL: Not no dissection but no type C dissection.

DR. DEWEESE: No class C?

DR. ANSEL: Yes.

DR. DEWEESE: So, this is a group of patients --

DR. ANSEL: Which is what you would expect. This is a very focal stenosis group. This is what you would expect. In fact, I thought that 10 was high because this is a very focal stenosis group that should respond very adequately to angioplasty at least early on. The fact that this group, even when we removed the 10 patients with suboptimal results, still had 3 patients that had subacute closure. That still gives me great concern, and it is one of the reasons that trying to go back and formulate a study as the original iliac studies would be nearly impossible because, as you saw, even with the study up and running clinicians are not willing to put the patients at risk and leave a suboptimal result for that.

DR. DEWEESE: Okay, but there were 10,

only 10 patients who required stents in the PTA group.

DR. ANSEL: Yes.

DR. DEWEESE: And, by the same definition, you would have had to have 50 or 60 have stents -- whatever, 69.

DR. ROSENFIELD: Can I just clarify that? The crossovers were patients not with a suboptimal balloon angioplasty result, they were patients who had threatened closure.

DR. DEWEESE: That is suboptimal.

DR. ROSENFIELD: Well, suboptimal by the definition they used as greater than 50 a percent residual stenosis, but we didn't really measure how many patients in the whole group of PTA patients had suboptimal results versus how many crossed over. I think there were probably a greater number that had a suboptimal PTA result than the number that crossed over. I think there is a difference between the two.

DR. DEWEESE: I just thought it might have helped you if you had compared a similar group of PTA people with the total group --

DR. ROSENFIELD: Yes.

DR. DEWEESE: -- rather than comparing it

differently.

DR. ROSENFIELD: There is no question that this retrospective review based on case report forms that were reported at the time by the investigators -- of course, nobody went back and corrected the data or anything.

DR. DEWEESE: Sure.

DR. ROSENFIELD: It was using original case report forms. There is no question that it is bound by some constraints, as is the trial in general because it didn't go to completion. But, again, as a clinician as are many of you, I look back at this and I say the stent was a winner all the way around here. If you assume a strategy where you were enrolling that patient for a stent you were guaranteed of a good result, 85 percent plus clinical long-term patency, number one. Number two, you could do that with a very effectiveness and low rate of complications, an excellent safety profile.

Contrast that -- and I am standing back here as a clinician and looking at this, contrasting that with the balloon patients, the balloon patients had also a very good long-term clinical outcome, slightly less but no significant

difference. But, that was at the expense of a four-fold greater statistically significant difference in complication rates and longer balloons, longer inflations. Those are the reasons that probably account for the increase in complications.

But the fact is that no matter how you look at it from a clinician's standpoint, it is much more straightforward to just do the stent group if you have the choice. And, I think that is reflected in the behavior of the investigators as the trial progressed and more of these off-label stents became available. I mean, let's face it, we acknowledge that there is a need for a stent at least for suboptimal results. I mean, if this stent is not approved, so be it but the fact is that the clinicians out there are still going to continue to do stenting for suboptimal results. They will just use off-label stents.

So, from my standpoint, I think this trial, for what it does present, is a very good case for at least having a stent available for suboptimal results and, not only that, it might actually present a good case for just going the route of stenting because you can do it with a

better safety profile.

DR. KUNTZ: I just want to address the analytical issue because I think your points, Dr. DeWeese, are very important. We didn't have the opportunity to do the appropriate analysis here. The best analysis for looking at suboptimal would have been to do an equal definition for both sides. Unfortunately the way the trial was run, we only had a protocol mandated angiogram after the balloon angioplasty in the stent arm, not after the primary angioplasty on the balloon angioplasty arm. So, we weren't able to look at the same level of suboptimal results and compare them. That is why we don't have 60 patients; we did the whole group.

The way that this evolved was that this was a prospective trial aiming to look at two strategies and compare them head-to-head. The results were the same in the endpoints. There were some subtle features to suggest that this did have some utility.

One of the burning questions was if this stent does provide a nice value for patients that don't have good angioplasty results, like it did in the 10 patients crossed over, was there any worse performance in patients who had stents for that

indication compared to stents for elective use? So, we elected to pick some cut point that would break up the stent group into two groups. If we just picked the 10 patients overall it would be underpowered. So, we took some level of complications that took about half the patients and put them in a suboptimal classification to compare them to the overall stent group. That was the attempt. We compared them with the balloon angioplasty group overall with the bail-out and the stent group overall. There was no difference.

And, the only conclusions from that suboptimal analysis is that if look at the stent performance in cases that weren't quite as good or even worse with balloon angioplasty up front, their performance overall was equivalent to the stents used electively and that the stents tended to equalize out the complications up front. So, the thresholds were maybe lower than we would use for the stent crossover, to be sure. It was done in order to get a more robust group to compare up front, and the limitations that both you and Dr. Roberts have pointed out about doing the head-to-head comparisons and prespecified are absolutely correct, but it was the best attempt to look at

some value of the stent overall.

DR. DEWEESE: Just one other thing, I am sure there are different ways of interpreting the final results of those 10 crossovers, but one way is that you could just say that there were 3 that did require immediate revascularization within 9 months and that there were 5 that either had developed a greater than 50 percent stenosis or had intermittent claudication. Then, there were 2 who were asymptomatic. This leaves you with just 20 percent who, by the end of the 9 months, showed evidence that they had improvement by the procedure. Now, there might be other discussions of the results.

DR. ROSENFIELD: I think you are absolutely right. I take at face value what you say, but the key is that for the investigator who is in that position of being faced with a critical limb situation, you know, you get the patient out of the tight spot and then you put them into a more elective situation. So, you are correct about the assessment.

DR. DEWEESE: I have no other questions now. Thank you.

DR. FREISCHLAG: I was impressed in

looking at the adverse events that quite a few of those patients were quite elderly, and my question was how many patients were over the age of 80 and how many were in the 70s? Your mean ages are late 60s but, to me, it seemed like a lot of the adverse events were in old patients.

DR. LABOUNTY: We didn't break that data down.

DR. FREISCHLAG: Was there any attempt during the trial to alter risk factors in these patients, such as to suggest to quit smoking or to tell them to exercise?

DR. ROSENFIELD: I will address that just from the standpoint of being one of the clinicians involved. Certainly, in our institution -- and I don't think we monitored that at every institution but certainly in our institution these patients are very rigorously followed. In fact, one might say that our patients in trials get the most aggressive attention to everything -- risk factor modification, and it is a very important point. But, I am not sure that that was within the purview of the trial, to monitor how much of that was being done across the board at every site.

DR. FREISCHLAG: The reason for my

question is, as you know, natural history data has it that this disease, as 80 percent in each of your groups were claudicators, a lot of them are treated just with that. They don't get stents, angioplasty, bypasses. They just say, "stop smoking; start walking and I'll see you in six months." Even though it seems we are ignoring them, it may actually work and not hurt them. So, I was interested to know if you were doing the same thing. Also, 80 percent of your people were still smoking when these procedures were done and I wonder how many were smoking when you got done with them.

DR. ROSENFIELD: Actually, 80 percent refers to a history of smoking. I don't think most of them were smoking at the time of the procedure but I don't have that data. That 80 percent reflects a history of smoking.

With respect to your question about risk factor modification and medical therapy, it is hard to address that because the trial was not a comparison between medical therapy and interventional therapy for claudication. We encouraged sites to only enroll patients who they were intending to intervene on in the first place.

So, we presume that they had already made a decision that in that particular patient's case there was an appropriate indication for intervention. In fact, the requirements for enrollment were certainly highly symptomatic claudication. It is difficult to monitor that, as you know.

DR. FREISCHLAG: I think it may have some impact when you look at outcome of what you do. Certainly, when we do bypasses, there is some data to show that unless some of the risk factors are altered our bypasses don't do as well. Certainly, if you are going to be doing dilatations and stents in smaller vessels, altering risk factors may actually be almost as important as the person standing there with the balloon.

DR. ROSENFIELD: Equally, if not greater. Not just for the purposes of preserving what you do but also for the purposes of reducing mortality and morbidity from other causes, namely, most of these patients die of coronary-artery disease. We know that. So, the point is well taken.

DR. FREISCHLAG: The reason for those questions was when you look at objective data, at least when I was looking at it, did these patients

get better or not, and not just surveys that say, "do you feel good?" your mean pre-procedure ABI was really equal across the groups at 0.6 to 0.7. Then, when you looked at your post-procedure ABIs, they were around 0.8 but the change in ABI actually really impressed me, that the only change in ABI at 9 months in all groups was around 0.1 and the error for that test is 0.1. When you do ABIs on patients, if you see them in follow-up if they get a 0.5 and they see you and they are at 0.6, you say it is sort of the error of the test. So, I guess my question is did anybody objectively get better? I know you didn't use treadmills or maximum walking distance, and things but, to me, the ABIs at 9 months are interesting but perhaps not real impressive in any of the groups. I am in section 3, page 14.

DR. ANSEL: From our slides -- I guess this is a backup slide but the change in ABI from baseline and 9 months was 0.19 versus 0.08 for the angioplasty group. At least in our institution, usually 0.15 is considered a significant change.

DR. FREISCHLAG: Well, you are barely there and in one of the groups you are not. I guess I was impressed that the magnitude of

difference with the images you show wasn't more. To me, when you look at the adverse events there were some patients who didn't have any change in their ABI and that is probably why your difference is low. Some of your adverse events, when you described them to us -- their ABI didn't change; a couple of them went down and, therefore, perhaps that is the reason that your magnitude of change is a little lower than I would expect in someone who would improve.

DR. ROSENFIELD: I actually think that an ABI changing from 0.69 to 0.92, which is the acute changes, is quite significant. That is certainly well within the Rutherford descriptions of improvement, and so on, that one would expect or hope to achieve with an intervention. In fact, the fact that there is persistent 0.19, in the stent group at least, improvement at 9 months -- we actually thought that was pretty reasonable. As you know, these patients have multi-level disease, most of them. As you pointed out, they are elderly and their vascular involvement is not just at one level. So, for some of them the fact that their ABIs are at 1.0 is a reflection of the fact that they have multi-level disease often in popliteal

involvement. To me, the ABI is only a surrogate endpoint. I mean, it is one hard thing you can hang your hat on but seeing thousands of these patients, I am often impressed that there may not be a change in ABI but there is a change in symptom pattern. So, actually the fact that there is a 0.19 improvement in ABI I thought was a pleasant surprise. So, I actually look at that from the other perspective but that is just my opinion.

DR. FREISCHLAG: Well, when you look at claudication, there are objective ways to do it and the one you give us is ABI. If you want to use getting better, most people use maximum walking distance or absolute walking distance and put it in there so you can get your teeth into it and bite it, saying, yes, they went up 30 percent or 50 percent, like with the pentoxifulline trials and cilostazol trials. You didn't give us that so the one thing I am grabbing on is the ABI.

DR. ROBERTS: They actually did give the maximum walking distance and actually, interestingly enough, although there are certainly very small numbers which is obviously a part of the problem with this, the PTA patients did better. There are two tables. One is table 25 under all of

the CBA-C analyses. The other one is table 20 under the subanalysis. Then, on table 25, the maximum walking distance, there was actually slightly more improvement in the PTA group. This is the randomized study. The maximum walking time also increased slightly. Again, I think it is very hard to know because there are such small numbers. The same seemed to be true with the patients who were in the suboptimal group. It is a little bit less in terms of their distances and also in terms of their time. But, you know, I think it is very difficult with the small numbers. That is one of the problems.

DR. FREISCHLAG: I apologize if I missed that.

DR. ROSENFIELD: There is a lot of data here, but I do think that the numbers are very small. I will be honest, as a person who actually was instrumental in writing this protocol at the outset, I recognize the importance of that very identifiable endpoint. It was difficult in the conduct of a very large, multi-center, randomized trial to get all of that data. As a result, the numbers are quite small and I think based on that it is hard to say anything.

DR. ANSEL: If I can interrupt for one second, the best group to look at in this trial is probably the roll-in patients. The reason that is, that was early on in the trial when all the investigators were hyped up and you were probably able to get patients into the walking study pre- and post-procedure. I think it was almost everybody. And, the degree of change, if you look at maximum walking time, is as good, if not better, than cilostazol per patient who improves. But the number of patients that report subjective improvement -- cilostazol was down around 50 percent; it was over 93 percent. So, in that group of claudicants, if you look at them both in walking time and subjective time and ankle-brachial index, their degrees of change are the same as the successes in the cilostazol studies.

DR. FREISCHLAG: Again, I would just caution -- they all want to make us feel good, our patients, and therefore they are going to tell us they are better. You really have to have the data.

DR. ROSENFIELD: But the thing is that for cilostazol 50 percent of patients said, "I didn't get better."

DR. FREISCHLAG: Right, but to look at

your trial though what I am worried about a bit is the 9 months and when you look at SFA angioplasty in retrospective studies in the next year, if there is a chance, they are not going to do quite as well. They are still on a risk level of failure or restenosis and you worry that this is probably the best they may be for a bit so you just want to make sure that you are seeing an actual difference. And, as a reader, someone who is not a participant, I was stretching a little bit to find the objective one. It is great they say they feel better. We all want them to feel better but for reporting standards we do like to see it a little bit more tight.

DR. ROSENFIELD: You would have to agree though that based on the Rutherford categories of reporting standards there is clearly a significant difference, 0.19 would be considered in anybody's book, I think, as a statistically significant improvement in ABI.

DR. FREISCHLAG: Yes, I think on an average it may be but I was concerned. Again, I haven't gone through each one of your patients to see who was what in what, but when you look at your adverse events there were some patients whose

adverse event was in their improvement at ABI but there wasn't any. So, I think you actually could have had a better one if each patient did improve, like 0.6 to 0.9 but I guess I am worried not all of them did otherwise your improvement would be 0.3 and then I would be real impressed. So, I think some of them didn't. You know, I am a surgeon and some of my bypasses don't improve as much as I want either for reasons you said, but you are right, they are notable but I am not sure they are as impressive per patient as I think I would have liked to be.

DR. ROSENFIELD: Your point is well taken. It is a good point. The other thing is to address your concern about the difference in walking time. Even though it is small numbers, again just to review and reiterate, I don't think we can claim from this trial that there is a difference in the primary endpoint. We have already acknowledged that there is not a difference in the primary endpoints between the PTA and the stent group.

But, remember that that group -- it is not fair to do this but I am going to take a little liberty here to say that if you had the 10 patients that crossed over, you can't assume necessarily

that they would have all had bad outcomes and they would have had complications and so on, but it is not a difficult stretch to say that for an investigator who has been told please don't cross anybody over unless they are really in a tight situation, it is not too much of a stretch to presume that those patients probably would have had poor walking times, poor ABIs if they had not crossed over.

So, I think what we are seeing is -- especially when there are small numbers in the overall trial, we are probably not doing justice to ourselves if we don't acknowledge that. For example, to push that one step further, and maybe I am talking a little poetic license here as a clinician but I am going to do it anyway, that 8.4 percent complication rate at 30 days, that might have been even greater had we not had the ability -- that is the 8.4 percent complication rate including the crossovers. In other words, if you say some of those patients hadn't had the ability to cross over that 8.4 percent might have been something like 10 or 12 percent. Already it was statistically significant at 8.4 percent versus 1.9. So, I am looking at this and saying, well,

the ability to cross over -- we are not looking at a pure balloon angioplasty versus pure stent trial; we are looking at a balloon angioplasty trial versus stent trial for relatively short lesions and still preserving the ability to cross over in the extreme case where you are going to end up in the drink if you don't cross the patient over. So, you know, maybe some of these other issues -- the walking distance, the ABIs and so on, maybe they would have been more disparate had we not had that crossover potential. I don't know but I throw it out there as a possibility.

DR. FREISCHLAG: My questions were just trying to figure out if anybody got better and how much better they got. My other question has to do with your 9-month angiographic follow-up where only 50 percent got their angiograms. You explained it in your text, saying it was really hard to convince patients to have that done. Why do you think that was? I mean, that was part of the deal, wasn't it, when you signed up for the trial, to have that done so you could talk to us about that? I guess I was disappointed that didn't happen. Could you have done duplex scans or something to look at it if they didn't want to do an angiogram?

DR. ROBERTS: Could I also just add to that because duplex was supposed to be part of this trial and, yet, there were only 17 patients or something or other that got duplex scans. I was just curious, going along with Dr. Freischlag's question, if you weren't going to get angiograms on these patients, I mean duplex is a very non-invasive way that you can really look at these areas and get a pretty good idea of what is going on. I was just wondering why that wasn't done.

DR. ANSEL: I can only speak for our site, and I don't know what our percentage is exactly but the major reason was because they were feeling good and they didn't want to come in and subject themselves to another half a day in the hospital to get their angiogram. The vast majority of our patients were from out of town and the duplex scans in their hospitals would not have been adequate.

DR. ROBERTS: Because there were 10 patients in the stent group and 7 in the PTA group that got duplex recorded, and this is in the randomized patients. Let me look and see what it was in the other group -- it is 4 in the suboptimal group and 7 in the PTA group.

DR. ROSENFIELD: First of all, I think

that is a good point. I think if we were doing a trial now -- we learned a lot in this trial. Let me put all the cards on the table here. If you are doing a coronary angioplasty trial, and many of you have been involved in coronary angioplasty trials, it is a funny thing, I think there is a difference in attitude on the part of patients about coming back for follow-up angiography because they perceive that their heart is at risk and I think it is a little easier to get angiographic follow-up in coronary trials than we have learned to be the case in peripheral vascular trials. To require angiographic follow-up -- it has become evident that that is a very difficult thing to do. I know you see a lot of these patients and they are tough. They feel better; they don't want anything to do with the hospital anymore. Even though they signed that dotted line initially, you can't force them. You can't, you know, send the police officer out to drag them in for their peripheral angiogram.

I think perhaps that could have been recognized up front but, quite frankly, this the first prospective randomized, multi-center trial looking at SFA disease. I am not aware of any others that have gone to this extent to try to

stratify patients in a multi-center, randomized fashion. And, one thing we learned is that probably duplex is a better endpoint but that wasn't set out at the outset of the trial as an endpoint.

DR. ROBERTS: It was.

DR. ROSENFIELD: It wasn't the primary endpoint of the trial.

DR. ROBERTS: In 1997 Doppler color flow protocol was sent. I mean, that was pretty much at the beginning of the trial, it seems to me.

DR. ROSENFIELD: I guess it wasn't perceived as the primary endpoint and, therefore, I am not sure, if you will, how strict people were about getting it.

DR. FREISCHLAG: Well, even if your numbers are small, if you have more objective data it is so much easier for us to ascertain if they are getting better. I am just looking for more hard data. I follow only legs, not hearts, and they all want to feel better but I think for watching them down the road a duplex scan would be very important, especially if you follow these patients another year. I think that is all of my questions.

DR. TRACY: We will take a ten-minute break, if we could regroup here about 11:10 or so.

[Brief recess]

DR. TRACY: I want to call this meeting back to order.

MS. MOYNAHAN: I just want to mention for the record that Bob Dacey, our consumer representative, couldn't make it today due to being snowed in, in Colorado. I am going to put Mike Crittenden on the spot and have him introduce himself since he didn't get a chance to do that earlier.

DR. CRITTENDEN: I apologize for the delay. My name is Mike Crittenden and I am a cardiac surgeon at the VA in Boston and faculty of the Harvard Medical School.

DR. TRACY: I guess I was next in line here to pick up with a few questions. It strikes me that there is sort of a lot being hung on the fact that there is in your presentation slides an 8.4 percent complication rate at 30 days in the PTA group versus 1.5 in the stent group from the original study. I was curious -- I was trying to find that original data, how were the acute closures counted? It looks like they were double

counted so an acute closure was also, I assume, the same people that were getting the acute revascularization. So, if there were 3 acute closures there were 3 acute revascularization, which added up to 6 of whatever the number of acute complications. Did I read that right?

DR. LABOUNTY: They weren't double counted. There were 3 abrupt closures which were classified by the Clinical Events Committee, which were 3 of the crossover patients which were identified by them as true abrupt closures. There were 3 subacute closures that also did have a TLR within 30 days in that was the major complication rate, along with the 3 renal failures, 1 amputation and 1 major bleed.

DR. TRACY: So, those were different people?

DR. LABOUNTY: Yes.

DR. TRACY: Okay. Then, I am wondering how much one month buys you because by 270 days it looked like there was not a distinguishable difference between the two groups. Is that correct?

DR. LABOUNTY: In long-term MACE there was not a statistically significant difference after

270 days. I think it was the acute complications.

DR. ROSENFIELD: Well, they were different endpoints. One was MACE and one was a composite of MACE and the kinds of things that you expect might be potential complications for a patient undergoing an acute intervention. So, they were slightly different endpoints.

DR. TRACY: I understand what you are saying. They are different endpoints but they are not different. The results in the two groups are not different at 270 days. So, there is something that happens within the first 30 days that we are sort of being asked to consider as being so clinically critical that it would make sense for this device to be approved for use, yet, by 270 days there is no difference. I am not sure what to think about that but that is just kind of a noticeable thing.

DR. LABOUNTY: The renal failures, the amputation and the major bleed are not included in that 270-day MACE rate. So, that is a separate endpoint.

DR. ROSENFIELD: Yes, part of the issue is that by treating at least some of those patients with stents to get them out of the situation of

abrupt closure, you then ameliorated the situation so that by 270 days. I am not sure to what extent but to some extent you equalize them by treating them acutely with a stent. Does that make sense? You know, we identified a series of problems that happened within 30 days. Some of those problems, not all of them, were recovered with stents, if you will, and then by 270 days you wouldn't expect to see a difference.

DR. TRACY: Okay. In that 8.4 percent, which I think is 11 patients, how many of those were crossover patients?

DR. LABOUNTY: Three of them were.

DR. TRACY: Three of them were?

DR. LABOUNTY: Yes, and those were the three abrupt closures that were classified as such by the Clinical Events Committee.

DR. TRACY: So, the abrupt closure was within the lab and then they had the stent as a rescue.

DR. LABOUNTY: Yes.

DR. TRACY: Thank you.

DR. LABOUNTY: So, that really would not include the other 7 potential ones. If they did not have the stent, it is really an unknown as to

what would have happened out to 30 days.

DR. ROSENFIELD: Those are the patients that I previously mentioned. We don't know what would have happened to them -- the other 7 patients, we don't know what would have happened to them if they didn't have a stent but we can presume, I think, that it wouldn't have been good things. It may or may not have been bad things but probably those patients, had they not crossed over, might have further increased the discrepancy between the two groups.

DR. TRACY: I think for those three patients presumably something bad would have happened because at that point where they abruptly closed probably the procedure was fairly far along, and that was the point at which something more had to be done. The vessel is now closed; they have been dilated several times, or whatever had taken place up to that point. What I am trying to look at is how do I understand these 70 people who were never intended only to have angioplasty and, therefore, all of the sort of parameters that we can look at objectively as to how much work was done before the stent was placed, how can we compare that? They are not really comparable to

those three who had the abrupt closure after, presumably, fairly extensive work, nor are they really comparable to the people who would have had more extensive work done to accomplish a successful angioplasty. So, they are just sort of there. The intent was always to put a stent in these people and I am not sure how to make a comparison with them and anybody else in this study.

DR. ROSENFIELD: I can only repeat what Dr. Kuntz has already actually stated pretty clearly, which is that, yes, this is a retrospective analysis of these patients in an attempt to try to identify what patients don't look good after an initial balloon angioplasty. It wasn't a prospective attempt to try to make these patients do as well as they could with balloon angioplasty before crossing them over to the stent. So, you are right.

DR. TRACY: The indication that you are looking for is for suboptimal results, but we are being asked to take a transient point in time and translate that into a suboptimal result outcome.

DR. ROSENFIELD: I think there are a couple of points to be made. Number one, the size of the balloon that was used for the pre-dilatation

was the full size of the vessel. In some cases you under-dilate the vessel before you go ahead and stent the vessel. In these patients the same size, and the statistical analysis actually showed that, there was a 1.1 to 1 balloon to vessel size ratio. The initial balloon that was used was a full sized balloon. So, the suboptimal result after that initial dilatation was using a full size balloon. That is number one.

Number two, what it says is that the initial balloon inflation did not accomplish what you came there to do. So, at the very least you can say that in those 70 patients the initial balloon treatment did not accomplish what you wanted it to do. Therefore, if you were then to say that patient is going to get ballooned and there is no stent available on the market or off the market, then you are going to have to repeat that balloon as many times as it takes to get as good a result as you can and hope that you get a good result. Whereas, if you are going to stent, then you just move directly to the stent; you put the stent in; post-dilate it and you are done.

So, you are right. How do you analyze that? I don't know. I mean, as a person

objectively looking at this I share your concern that it is not really the same thing as bailing out, if you will, after multiple, multiple balloon inflations, but it is an indication that if you are going to not have a stent available you are going to have to repeat the balloon and repeat it as many times -- and in some percentage of cases that is going to be a lot of times; in some percentage of cases that may just be one or two more balloon dilatations.

DR. TRACY: How do you train people to do this? At what point do you say, okay, now you have a suboptimal result; go ahead and put in a stent? Because that could range from anywhere from somebody just making a half-hearted attempt to blow up a balloon and say, "oh, that's no good; let me go ahead and put in a stent," versus somebody going through 50, 60 minutes of fluoro time and very extensive attempts, and bringing the patient closer and closer to an adverse event before they cross over to a balloon. How do you train somebody to know at what point it is the correct time to consider it suboptimal and to move on?

DR. ANSEL: Certainly from a clinical standpoint, I think that you don't half-heartedly